THE STRUCTURE OF MUSK TIBETINE AND MUSK KETONE

BY

THEODORE GERARD KLOSE

B.S., Elmhurst College, 1943
M.S., University of Illinois, 1944

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Introduction

Musk Ketone, prominent among the early synthetic musks, was prepared by acetylation of 5-*t*-butyl-*m*-xylene followed by nitration of the resulting ketone. The structure was thought to be 6-*t*-butyl-2,4-dimethyl-3,5-dinitroacetophenone (1). Musk Tibetine, of more recent origin, was prepared from the same parent hydrocarbon by chloromethylation followed by dehalogenation and nitration. The structure of this molecule was given as 6-*t*-butyl-3,5-dinitropseudocumene (2).

Fuson, Denton and Kneisley (3), while studying the coupling action of Grignard reagents on 4-*t*-butyl-2,6-dimethylbenzyl chloride, found evidence that the structure of the hydrocarbon precursor of Musk Tibetine is 5-*t*-butylhemimellitene and not 6-*t*-butylpseudocumene.

Since acetylation and chloromethylation are modifications of the Friedel-Crafts synthesis, it was to be expected that they would yield derivatives having the same orientation of groups. This consideration made it appear that the structure of Musk Ketone likewise might be wrong. The purpose of the present research was to determine the structures thus called in question.

Discussion of Results

The correct structure for Musk Tibetine has been proved to be 5-*t*-butyl-4,6-dinitrohemimellitene and, similarly, Musk Ketone has been shown to be 4-*t*-butyl-2,6-dimethyl-3,5-dinitroacetophenone. The evidence for the symmetrical structures is based on reactions relating the musks to 5-*t*-butyl-2-nitro-*m*-xylene. This compound has an unquestioned structure and can be converted to the corresponding amine

and eventually transformed to 2-bromo-5-*t*-butyl-*m*-xylene. The bromo compound was used for an unequivocal synthesis of Musk Ketone by converting it to 4-*t*-butyl-2,6-dimethylbenzoic acid by the Grignard method. The acid chloride, prepared by the conventional procedure and treated with dimethyl cadmium, gave a 30 per cent yield of the desired 4-*t*-butyl-2,6-dimethylacetophenone. The acid chloride was converted to 4-*t*-butyl-2,6-dimethylbenzaldehyde whose dinitro derivative has the same physical constants as Musk Aldehyde, which had been given the incorrect, unsymmetrical structure by Baur and Bischler (4).

Musk Cyanide, the dinitro derivative of 4-*t*-butyl-2,6-dimethylbenzonitrile, was prepared and found to be identical with the compound of Baur. However, the parent nitrile was found to melt at 64.5-65.5° whereas Baur reported a value of 88° (5). Three independent methods were used to prepare the nitrile: (1) the Sandmeyer reaction on 4-*t*-butyl-2,6-dimethylaniline, (2) the Rosenmund-von Braun reaction involving the use of 4-*t*-butyl-2,6-dimethylbromobenzene and (3) dehydration of the oxime of 4-*t*-butyl-2,6-dimethylbenzaldehyde.

The proof of structure of 5-*t*-butylhemimellitene, the hydrocarbon from which Musk Tibetine is prepared, rests on two different syntheses. The first involved the conversion of the Grignard reagent of 4-*t*-butyl-2,6-dimethylbromobenzene (6) to the hydrocarbon by means of dimethyl sulfate and the second was the dechlorination of 4-*t*-butyl-2,6-dimethylbenzyl chloride.

Chloromethylation and acetylation of 5-*t*-butyl-*m*-xylene were shown to involve the *para* position in relation to the *t*-butyl group by the conversion of 4-*t*-butyl-2,6-dimethylacetophenone to 5-*t*-butyl-2-ethyl-*m*-xylene by the Clemmensen reduction. The same compound was obtained by treatment of 4-*t*-butyl-2,6-dimethylbenzylmagnesium chloride with dimethyl sulfate. Chloromethylation and acetylation,

processes which are involved in the preparation of Musk Ketone and Musk Tibetine, are thus shown to occur at position 2, proving that the musks have the symmetrical structures.

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